DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Central Region 93168-1

Food and Drug Administration
Waterview Corporate Center
10 Waterview Blvd., 3rd Floor
Parsippany, NJ 07054

Telephone (973) 526-6005

March 11, 2002

WARNING LETTER

CERTIFIED MAIL-
RETURN RECEIPT REQUESTED

Mr. Robert Chabora
President, Drug Development & Technology
Berlex Laboratories, Inc.
300 Fairfield Road
Wayne, NJ 07470

File # 02-NWJ-18

Dear Mr. Chabora:

During a January 3 through February 4, 2002 inspection of your drug manufacturing facility located at 300 Fairfield Road, Wayne, New Jersey, investigators from this office documented significant deviations from current Good Manufacturing Practice (cGMP) Regulations as delineated in Title 21, Code of Federal Regulations, Parts 210 and 211.

The inspection revealed the Quality and Production systems employed during the manufacture, processing, packing, or holding of your Quinaglute Dura-Tabs® (quinidine gluconate extended release tablets, USP) prescription drug product do not conform with cGMP. Therefore, the product is adulterated within the meaning of Section 501(a)(2)(B) of the Federal Food, Drug and Cosmetic Act (the Act). Additionally, the product is adulterated within the meaning of Section 501(c) of the Act in that the quality and purity of the drug product differs from what it purports or is represented to possess since the filed specification for the products description does not include visible metal fragments on the surface of the tablet. The following are examples of the significant deficiencies regarding your firm's Quality and Production systems that were cited by our investigators:

1. Your firm's Quality Unit failed to prevent the release of six lots of Quinaglute Tablets that contained visible metal fragments which came from unqualified manufacturing equipment used during production. A visual examination of retain samples by our investigators and by representatives of your firm have confirmed that numerous tablets from these lots contain visible fragments of metal. The lots involved include #W00238, W00239, W00240, W10001, W10028 and W10029, and were manufactured between November 2000 and May 2001 having expiration dates between November, 2004 and May, 2005 respectively.

You acknowledge in your February 15, 2002 written response to the FDA-483 Inspectional Observations, that some of your Quinaglute tablets, "...might have a detectable/visible speck of metal derived from manufacturing equipment...." You explain that the source of the metal fragments found was from a refurbished piece of manufacturing equipment; specifically, a stainless steel [redacted] that had thin indentations of approximately 1/16 inch deep gouged into its exterior by a new stainless steel blade. Our investigators found that your Quality Unit failed to adequately evaluate the change in manufacturing equipment from a previously used carbon steel blade to the stainless steel blade. As a result, the new stainless steel blade was incompatible with the refurbished [redacted] and not only caused damage to the drum but "...nicks with small burrs" were gouged into the blade as well. Your investigation found metal shavings measuring as large as 3/4 inch long by 1/16 inch wide that were scraped off the [redacted] and into Quinaglute lot #W00239.

Please be advised that this office disagrees with the assertion and statement in your correspondence that the visual observance of metal fragments in prescription drug products is not, "...a significant deviation from cGMPs." In your correspondence, you also state that your Quality Unit conducted an investigation and all lots, "...were found to be in compliance with cGMPs, standard operating procedures and met specifications when released for distribution." This statement is misleading. During production of the next sequential lot of Quinaglute, lot #W10079, your Quality Unit saw metal fragments in the wax section again and initiated a second investigation that resulted in the rejection of the lot. This rejected lot was the first lot of Quinaglute manufactured after closing your first investigation. All seven lots used the "...softer..." stainless steel blade and the same refurbished Flaker drum. In the rejected lot #W10079, the pieces of metal were, "...approximately 5/32" in width, and ranged from approximately 1" to 3 ¾" in length." It should also be noted that lot #W10111, which followed the rejected lot, also had retain tablets containing visual contamination observed by our investigators. Your firm had switched back to utilizing the carbon steel blade during the manufacture of lot #W10111.

Your first investigation into this incident, dated May 23, 2001, stated there were, "...two thin scratches..." on the Flaker drum. Your second investigation initiated on May 31, 2001 and dated October 2, 2001 states that there were "...two deep horizontal nicks...and a thin shallow scratch..." on the drum. During the inspection, on January 24, 2002, our investigators actually observed four indentations, two horizontal nicks and other various gouges on the drum.

You have stated in your response that the USP "...considers some metal particles to be unobjectionable..." in prescription drug products and you refer to USP General Chapter <751> Metal Particles in Ophthalmic Ointments. Please be advised that the USP refers to particles in this chapter in the *micrometers* size and not in terms of *inches*. While it is generally understood in the pharmaceutical industry that normal wear and tear of manufacturing equipment may lend particulate matter to the products being produced, this type of particulate matter is not visible to the naked eye and is in the parts per million (ppm) or parts per billion (ppb) range. It is not acceptable to have visually observable contaminants in your finished dosage form as is the case with your Quinaglute product. It is the responsibility of your firm's Quality Unit to assure the identity, quality,

strength and purity of your products and to assure they meet all of their purported quality attributes. The quality standard you have set for your Quinaglute product does not include visible metal fragments on the surface of the tablet as an acceptable release specification.

2. The procedures and controls used by your Quality Unit are inadequate to assure the identity, quality, strength and purity of your Quinaglute product. For example, your firm's Quality Assurance Release Manager stated to our investigators during the inspection that approximately 5027 tablets were examined from lot #W00239 during in-process and Quality Assurance testing and only one tablet was found to have visual evidence of contamination. The batch size for this lot was [redacted] tablets. Our investigators examined the tablets from a single retain bottle of this lot containing 500 tablets and observed 9 tablets with visual contamination.

   Furthermore, even though [redacted] of the lot (approximately 84,000 tablets) was rejected by your metal detector during an added check for metal, your Quality Unit chose not to analyze any of the tablets for metal content. In fact, in your response, you state "...the high rejection rate can be attributed in part to false triggering of the alarm" on the metal detector.

   You have stated in your response that, "All of the actions taken by Berlex personnel...were in accordance with its internal procedures and cGMPs" regarding the metal contamination in Quinaglute. We disagree with this statement. Please be advised that your Quality Unit has failed to establish reliable controls and procedures to assure that your products meet all predetermined quality attributes. For example, your Quality Unit has failed to validate the rework procedure which was used in the manufacture of Quinaglute Lot #W90128. There is no data to demonstrate that the rework procedure, which includes the addition of more [redacted]; would yield tablets meeting predetermined specifications for the product. Additionally, your firm's procedure for hold time of in-process material states that material will not be held longer than 30 days prior to use. However, the in-process material [redacted] used in Quinaglute lot #W10111 was held for approximately 50 days and used without adequate testing to assure its uniformity.

3. Your firm failed to adequately qualify the [redacted] metal detector which is used in the manufacturing process of Quinaglute tablets. Specifically, this metal detector did not detect and remove a tablet containing a visually apparent metal fragment. In your correspondence, you confirm the lack of qualification of this piece of manufacturing equipment by explaining that your "...Quality Assurance [department] detected a tablet with a gray speck, appearing to be metallic" but, "This tablet was not detected or rejected by the Lock metal detector." Your firm's laboratory analysis of this tablet later revealed that the contaminant, "...was 316 stainless steel."

We acknowledge your intentions, as promised in your February 15, 2002 correspondence, to enhance your investigation procedure entitled "Product Occurrence Handling" as part of your corrective action plan.

The above items are not intended to be an all-inclusive list of deficiencies at your facility. It is your responsibility to ensure that the drug products you manufacture are in compliance with the Act and the regulations promulgated under it. Federal agencies are routinely advised of Warning Letters issued so that they may take this information into account when considering the award of government contracts.

You should take prompt action to correct deficiencies at your facility. Failure to implement corrective measures may result in further regulatory action without notice. These actions may include seizure of your products or injunction.

You should notify this office in writing within 15 working days of receipt of this letter of your corrective action plan to address the deficiencies at your firm. If corrective actions cannot be completed within 15 working days, please state the reason for the delay and the timeframe within which corrective actions will be completed. Your reply should be addressed to the New Jersey District Office, Food and Drug Administration, 10 Waterview Blvd., Parsippany, New Jersey 07054, Attn: Joseph F. McGinnis R.Ph, Compliance Officer.

Sincerely,

Douglas I. Ellsworth
District Director
New Jersey District